COMPENSATORY HYPERTROPHY OF THE CONTRALATERAL KIDNEY AFTER UNILATERAL URETERAL LIGATION

By S. E. DICKER and D. G. SHIRLEY*

From the Department of Physiology, Chelsea College, London, S.W. 3

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SUMMARY

1. The ligation of one ureter is accompanied by compensatory hypertrophy of the contralateral kidney.

2. The rate of growth of the contralateral kidney after ligation of the opposite ureter is similar to that observed after unilateral nephrectomy.

3. Ligation of one ureter produced ipsilateral hydronephrosis.

4. The development of hydronephrosis was accompanied by a marked increase of DNA, suggesting hyperplasia, and of the rate of anaerobic glycolysis, while the rate of oxygen uptake decreased, especially in the cortex.

5. During compensatory hypertrophy of the contralateral kidney, after ligation of the opposite ureter, there were increases of RNA/DNA ratios and of oxygen uptake, especially marked in the cortex, and in every respect similar to those observed after unilateral nephrectomy.

6. Ligation of one ureter resulted in an increase of glomerular filtration rate of the contralateral kidney similar to that observed after unilateral nephrectomy.

7. The mechanisms of contralateral renal hypertrophy after ligation of one ureter and after unilateral nephrectomy are discussed. It is suggested that in both cases the prime mover to compensatory hypertrophy is the increase of glomerular filtration rate.

INTRODUCTION

Since kidney weights bear a constant relation to body surface area, and hence to weight, in dogs (Stewart, 1921), rabbits (Taylor, Drury & Addis, 1923), rats (MacKay & MacKay, 1927; Dicker, 1949), man (MacKay, 1932; Wald, 1937) and in a variety of other mammals (Smith, 1951) it is difficult to see how such a relationship could be maintained in the absence of a control system (Bayliss, 1966). After unilateral nephrectomy there is usually compensatory growth of the contralateral kidney. Though the number of nephrons remains unchanged (Smith, 1951), in rats com-

pensatory hypertrophy goes on for weeks after renal homoeostasis has been restored (Dicker & Shirley, 1971*b*). Whereas in adult rats and mice compensatory renal growth appears to start almost immediately after the removal of one kidney, there is evidence that in adult higher mammals like man (Heideman & Rosenbaum, 1970) the onset of renal hypertrophy may be delayed by several months, though renal homoeostasis is normal a few days after the operation (Franklin & Merrill, 1960; Fida & Cerruti, 1960; Ogden, 1967).

　　The fact that renal hypertrophy does *not* occur when the opposite ureter has been severed (Goss & Rankin, 1960; Simpson, 1961; Royce, 1963) but does occur when it has been ligated (Hinman, 1922; Herlant, 1948; Goss & Rankin, 1960; Benitez & Shaka, 1964; Mason & Ewald, 1965) as well as after unilateral nephrectomy, makes it unlikely that compensatory renal growth can be attributed to an increased excretory load. Since the physiological pathways by which the remaining kidney enlarges following unilateral nephrectomy have still not been entirely elucidated, it was thought that an investigation into the mechanisms of renal hypertrophy following ligation of the opposite ureter might shed some light on the problem.

METHODS

Adult white male rats of about 200–250 g body wt. were used. Under ether anaesthesia, through a lumbar incision, either the left ureter was exteriorized and ligated, or the left kidney was removed. In sham operated animals the left ureter or the left kidney was manipulated but otherwise left intact. Animals were killed 1, 2, 4, 7 and 14 days after the operation.

Estimation of renal hypertrophy. Weights of right kidneys from animals with the left ureter ligated were compared with those of right kidneys from unilateral nephrectomized rats and with those of sham operated animals. Kidney weights were expressed as g/100 g body wt.

Estimation of oxygen uptake and anaerobic glycolysis. Rates of oxygen uptake (Q_{O_2}) or of anaerobic glycolysis ($Q_{CO_2}^{N_2}$) were measured in slices from the renal cortex and medulla, using a Warburg apparatus, as described previously (Dicker & Shirley, 1971*a*). Values for Q_{O_2} and $Q_{CO_2}^{N_2}$ were expressed as μl./hr.mg dry weight.

Estimation of DNA and RNA. The methods were the same as those used by Dicker & Shirley (1971*b*), the amounts of DNA and RNA being estimated in the renal cortex and medulla separately, and expressed as μg/mg dry wt.

Glomerular filtration. This was estimated in the usual way in animals which had received 5 ml. H_2O/100 g body wt. by stomach tube and which were injected subcutaneously with 2 ml./100 g of a 10 % solution of inulin, 30 min after water administration. The period of urine collection was exactly 15 min from 60 to 75 min after the injection of inulin (Dicker & Heller, 1945; Friedman, Polley & Friedman, 1947; Dicker & Shirley, 1971*b*).

Estimations of inulin and Na in plasma and urine. These were estimated as described in Dicker & Shirley (1971*b*).

Diet. All animals were fed on a standard diet containing approximately 18 % casein and yielding about 300 cal/100 g.

In rats with a ureter ligated, there was early distension of the ureter which extended progressively to the renal pelvis. Two weeks after ureter ligation, the obstructed kidney was unusually large and often looked paler than the contralateral kidney; when cut open it showed signs of hydronephrosis.
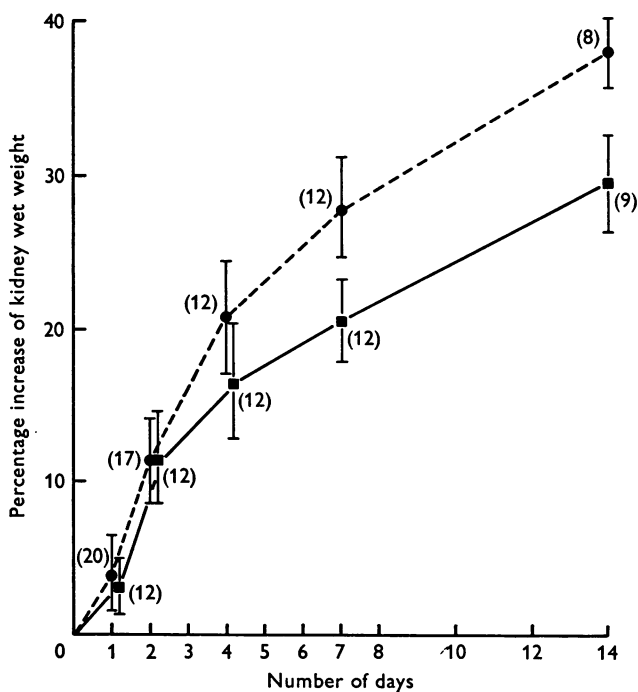

Fig. 1. Rate of compensatory renal growth after unilateral nephrectomy and ureter ligation. Percentage increase of the contralateral kidney wet weight: ■—■ after ligation of the ureter of the opposite kidney, ●----● after unilateral nephrectomy. Vertical lines represent s.e. of mean. Figures in brackets: number of experiments. Abscissa: number of days after operation. Ordinate: percentage increase of kidney wet weight.

As a result of ligation of the left ureter, the contralateral right kidney increased in size. Its rate of growth was not significantly different from that observed after unilateral nephrectomy (Fig. 1). The water content of slices from the cortex and medulla of the kidney with a ligated ureter increased markedly. Increases in water content of renal tissue have been observed after elevation of the ureteral pressure in dogs (Suki, Guthrie, Martinez-Maldonado & Eknoyon, 1971). In the contralateral kidney,

however, the amount of water in slices from the cortex and medulla remained unchanged (Table 1) as in sham operated animals.

Estimations of DNA and RNA showed that after ligation of the left ureter, the concentrations of DNA and RNA increased in both the cortex and the medulla of the obstructed kidney. Two days after ureter ligation, RNA/DNA ratios had increased from 1·25 to 1·51 in the cortex, and from 0·90 to 1·22 in the medulla (Table 2). In contrast, in the contralateral kidney, changes in DNA and RNA content were essentially the same as those observed in the renoprival kidney: i.e. in the cortex a marked decrease of DNA concentration, while in the medulla no significant changes were observed (Dicker & Shirley, 1971b).

TABLE 1. Comparison of water content of cortex and medulla of kidneys with a ligated ureter with that of cortex and medulla of contralateral kidney

Time since operation	Obstructed kidney		Contralateral kidney	
	Cortex	Medulla	Cortex	Medulla
0	76·0 ± 0·2 (15)	80·6 ± 0·4 (14)	76·0 ± 0·2 (15)	80·6 ± 0·4 (14)
1 day	79·7 ± 0·2 (10)	83·0 ± 0·5 (8)	75·9 ± 0·2 (10)	81·0 ± 0·6 (8)
2 days	80·2 ± 0·2 (10)	83·9 ± 0·4 (8)	75·7 ± 0·2 (10)	81·1 ± 0·6 (8)
4 days	81·3 ± 0·4 (8)	83·8 ± 0·3 (8)	75·6 ± 0·2 (8)	80·3 ± 0·3 (8)
7 days	81·9 ± 0·2 (13)	83·8 ± 0·3 (11)	75·8 ± 0·2 (13)	80·9 ± 0·4 (11)
14 days	81·7 ± 0·3 (10)	84·1 ± 0·3 (8)	75·8 ± 0·1 (10)	80·9 ± 0·3 (8)

Estimations of water content were made on slices from the renal cortex and medulla. Values are means ± S.E. In brackets, number of estimations. Values at time 0 are those obtained either from animals killed before the operation or from sham operated rats.

Rates of anaerobic glycolysis ($Q_{CO_2}^{N_2}$) were the same in control (non-operated) and sham operated rats. No changes of $Q_{CO_2}^{N_2}$ values were observed during compensatory hypertrophy of the contralateral kidney following either unilateral nephrectomy or ligation of the ureter of the opposite kidney. In the obstructed kidney, however, rates of anaerobic glycolysis increased markedly, especially in the cortex. In the cortex, $Q_{CO_2}^{N_2}$ increased from a pre-operative level of 1·83 ± 0·08 (10) μl./hr.mg dry wt. to 3·15 ± 0·16 (6) and 3·65 ± 0·17 (6) after 4 and 7 days of ureter obstruction, respectively; while in the medulla it increased from 7·06 ± 0·31 (10) to 9·26 ± 0·62 (6) μl./hr.mg dry wt. in 7 days.

The rates of oxygen uptake by slices from the renal cortex and medulla in control rats were similar to those found in sham operated animals. Twenty-four hours after ligation of the left ureter, there was a significant increase in the values of Q_{O_2} by slices of the cortex from both the ipsilateral and contralateral kidneys (Table 3); but, whereas the oxygen uptake in the

TABLE 2. DNA and RNA content of renal cortex and medulla in kidneys with ligated ureters and in contralateral kidneys

No. of days after operation	No. of animals used	Obstructed kidney						Contralateral kidney					
		Cortex			Medulla			Cortex			Medulla		
		DNA (µg/mg)	RNA (µg/mg)	RNA/DNA	DNA (µg/mg)	RNA (µg/mg)	RNA/DNA	DNA (µg/mg)	RNA (µg/mg)	RNA/DNA	DNA (µg/mg)	RNA (µg/mg)	RNA/DNA
0	12	14·50 ±0·21	18·04 ±0·13	1·25 ±0·02	18·87 ±0·31	16·91 ±0·21	0·90 ±0·02	14·50 ±0·21	18·04 ±0·13	1·25 ±0·02	18·87 ±0·31	16·91 ±0·21	0·90 ±0·02
1	6	14·48 ±0·20	21·63 ±0·39	1·49 ±0·02	18·47 ±0·35	20·24 ±0·18	1·09 ±0·01	12·90 ±0·13	17·43 ±0·08	1·35 ±0·01	19·63 ±0·21	16·47 ±0·16	0·84 ±0·01
2	6	18·28 ±0·71	27·32 ±0·15	1·51 ±0·05	22·80 ±0·50	27·70 ±0·37	1·22 ±0·02	12·22 ±0·21	18·44 ±0·12	1·51 ±0·02	20·00 ±0·37	16·88 ±0·37	0·85 ±0·02
4	6	23·21 ±0·27	30·43 ±0·21	1·31 ±0·02	24·63 ±0·37	28·89 ±0·37	1·18 ±0·01	11·35 ±0·12	17·25 ±0·12	1·53 ±0·02	17·97 ±0·20	16·45 ±0·41	0·92 ±0·02
7	6	22·76 ±0·83	27·96 ±0·61	1·23 ±0·03	23·95 ±0·86	25·25 ±0·31	1·06 ±0·03	11·82 ±0·17	17·36 ±0·12	1·47 ±0·03	18·48 ±0·31	16·60 ±0·37	0·90 ±0·02
14	6	21·58 ±0·33	25·90 ±0·06	1·20 ±0·02	21·32 ±0·57	21·95 ±0·13	1·04 ±0·03	11·03 ±0·17	17·15 ±0·08	1·56 ±0·02	17·23 ±0·94	15·97 ±0·58	0·93 ±0·03

Estimations of DNA and RNA are expressed as µg/mg dry tissue (cortex or medulla). Values are mean ± s.e. Values at day 0 are those of control rats.

cortex of the contralateral kidney continued to increase and remained elevated for up to 7 days after the operation, as had been observed in the renoprival kidney (Dicker & Shirley, 1971 b), in the obstructed kidney with a ligated ureter, the initial increase of Q_{O_2} was followed by a steady decrease (Table 3).

TABLE 3. Values of Q_{O_2} in renal cortex and medulla of contralateral and ipsilateral kidneys after ligation of the ureter of the ipsilateral kidney

	Q_{O_2} (μl. hr^{-1}.mg^{-1} dry tissue)			
Days after operation	Kidney with ligated ureter		Contralateral kidney	
	Cortex	Medulla	Cortex	Medulla
0	13.75 ± 0.17 (24)*	8.25 ± 0.26 (24)*	13.75 ± 0.17 (24)*	8.25 ± 0.26 (24)*
1	14.88 ± 0.39 (9)	8.94 ± 0.53 (9)	15.44 ± 0.21 (9)	8.42 ± 0.53 (8)
2	14.04 ± 0.45 (9)	7.83 ± 0.25 (9)	16.17 ± 0.41 (9)	8.73 ± 0.58 (9)
4	13.16 ± 0.37 (9)	7.28 ± 0.37 (9)	15.86 ± 0.20 (9)	8.48 ± 0.46 (8)
7	12.54 ± 0.39 (9)	6.97 ± 0.25 (9)	15.37 ± 0.21 (9)	9.21 ± 0.42 (9)
14	9.02 ± 0.49 (9)	6.10 ± 0.25 (9)	13.72 ± 0.29 (9)	8.74 ± 0.37 (9)

Values are means with their s.e. In brackets, number of estimations.
* Values for day 0 are those in control rats.

TABLE 4. Q_{O_2} per cell (estimated as Q_{O_2}/DNA; see text) of the cortex or the medulla of the kidney with a ligated ureter and of the contralateral kidney

	Q_{O_2} (μl.)/DNA (μg)			
Number of days after operation	Kidney with ligated ureter		Contralateral kidney	
	Cortex	Medulla	Cortex	Medulla
0	0·94	0·43	0·94	0·43
1	1·03	0·48	1·19	0·43
2	0·77	0·34	1·32	0·44
4	0·56	0·29	1·39	0·46
7	0·55	0·29	1·30	0·49
14	0·41	0·29	1·24	0·50

Figures are averages obtained from mean values of Q_{O_2} (Table 3) and of DNA concentrations (Table 2). Values at day 0 are those from sham operated animals; they do not differ from those of control rats.

Since the amount of DNA per cell has been shown to be constant (Vendrely, 1955; Malt, 1969) it is possible to calculate changes in Q_{O_2} per cell. This is represented in Table 4 for both the ipsilateral and contralateral kidneys. Whereas in the cortex of the contralateral kidney there is a marked increase of oxygen uptake per cell, in the hydronephrotic kidney, in spite of a significant hyperplasia as assessed by the increase of DNA (Table 2), there is a decrease in the amount of oxygen consumed per cell.

Filtration rate was estimated in the contralateral kidney only. On the assumption that in animals with both kidneys intact, the contribution to inulin and urine excretion is the same from both kidneys, values for inulin and Na clearance and for urine excretion were halved in sham operated animals. This allowed a comparison with the contralateral kidney of hydronephrotic rats. It will be seen from Table 5 that the results follow the same pattern as those described previously for the renoprival kidney (Dicker & Shirley, 1971*b*): i.e. an initial sharp increase in glomerular filtration rate and urine flow, which then decreased until by 7 days after the ligation of one ureter the glomerular filtration was stabilized at about 60–70 % above its pre-operative level, while Na excretion, expressed as percentage of Na reabsorbed from the glomerular filtrate, remained unaffected.

TABLE 5. Effects of ureter ligation on glomerular filtration rate (G.F.R.), urine flow, and Na reabsorption of the contralateral kidney

Days after ligation of ureter	G.F.R. ml. kg.min^{-1}	Urine flow ml. kg. min^{-1}	% Na reabsorbed from filtrate
0	3·294* ± 0·092	0·227* ± 0·023	99·7 ± 0·06 (12)
1	6·858 ± 0·863	0·370 ± 0·073	99·6 ± 0·07 (6)
2	10·538 ± 0·954	0·481 ± 0·084	99·7 ± 0·03 (6)
4	6·000 ± 0·686	0·367 ± 0·027	99·6 ± 0·04 (3)
7	5·538 ± 0·835	0·355 ± 0·017	99·8 ± 0·03 (5)

So as to give an estimate of the contribution by one kidney, values marked * were obtained by halving those actually measured. In brackets, number of animals. Values in sham operated animals did not differ from those obtained before operation (Day 0).

DISCUSSION

The present results, which show that the ligation of one ureter is accompanied by an increased growth of the other kidney, confirm previous observations by Hinman (1922), Herlant (1948), Goss & Rankin (1960), Benitez & Shaka (1964) and Mason & Ewald (1965). Since severance of one ureter or its anastomosis into the intestine does not promote growth of the contralateral kidney (Block, Wakim & Mann, 1953; Goss & Rankin, 1960; Simpson, 1961; Royce, 1963) while ligature of one ureter or unilateral nephrectomy results in hypertrophy of the opposite kidney, it is difficult to attribute the cause of compensatory renal hypertrophy solely to an increased excretory work load.

Krohn, Peng, Antell, Stein & Waterhouse (1970) have shown in the dog that 5 min after unilateral nephrectomy the renal blood flow in the contralateral kidney increased by about 30 %. This agrees with Rous & Wakim's (1967) observations, also on dogs, of a 30 % increase in the

clearance of p-aminohippuric acid, 24 hr after unilateral nephrectomy. According to Krohn et al. (1970) the onset of renal hypertrophy is the result of the haemodynamics of the aortic blood flow. Normally 50 % of the cardiac output goes to the renal arteries and the distal aorta below the kidneys, while 25 % of the cardiac output goes to the kidneys. After unilateral nephrectomy 12·5 % of the cardiac output would therefore be diverted to the opposite renal artery and distal aorta. Assuming that the usual distribution ratio of 2:1 between distal aorta and renal blood flow is maintained, then 4·2 % of the cardiac output would be diverted to the remaining kidney, which would amount to an increase of some 34 % of its blood flow, a figure which agrees very well with the measured increment. A similar, though not identical, approach to the problem has been suggested by Johnson (1969).

It has been shown repeatedly in acute experiments that the blocking of one ureter or the elevation of ureteral pressure produces an immediate increase of the blood flow to that kidney (Selkurt, 1963; Carlson & Sparks, 1970; Suki et al. 1971). It has been shown in experiments on rabbits that 24 hr after the obstruction of one ureter the blood supply to that kidney had decreased (Herdman & Jaco, 1950) and that after 1 week it had dropped by 60 % (Idbohrn & Muren, 1956). It is therefore likely that a similar decrease of blood flow to the hydronephrotic kidney occurred in the present experiments, as indicated by the sharp fall of the rate of oxygen uptake.

The question then is: can a prolonged decrease of renal blood flow be the cause of the hypertrophy of the contralateral kidney? Immediately after ligation of the ureter there is in the obstructed kidney a marked increase in DNA (Table 2) and in mitotic activity (Benitez & Shaka, 1964). The reason for the increase of DNA synthesis and cell division in the hydronephrotic kidney is still unknown. It is, however, of interest to note that a similarly marked cellular proliferation has been observed in the gall-bladder after ligation of the common bile duct. This mitotic activity could not be explained by a mechanical distension, since the filling of the gall-bladder with liquid paraffin failed to stimulate mitosis (Jacoby, 1953, 1959).

Goss & Dittmer (1969) have pointed out that the secretion of renin in a kidney with a poor blood flow may increase the production of angiotensin which in turn would stimulate the secretion of mineralo-corticoids by the adrenal cortex. According to Crane & Dutta (1963), Crane & Ingle (1964) and Moraski (1966) deoxycorticosterone promotes renal hypertrophy, and according to Forte & Landon (1968) aldosterone enhances the incorporation of orotic acid into RNA in the kidney. Recently, however, Vancura, Sharp & Malt (1971) have shown that using physiological doses of aldo-

sterone, there was no acceleration of synthesis of RNA in the toad bladder and added that 'some reports to the contrary may have been influenced by artifacts from bacterial RNA metabolism'.

In adult rats, kidney weights bear a constant relation to body weight. As rats continue to increase in weight with age, so do their kidneys. Such a close relationship between kidneys and body weight suggest the existence of a central control. Burch (1968) proposed a theory according to which the size of any organ is 'estimated' by a central comparator. He assumed that information from each organ, in the present case from both kidneys, reaches the central comparator and that in turn the latter sends signals to the organs. These views are very similar to those expressed by Bayliss (1966) in 'Living control systems', and more recently by Riggs (1970). According to Burch (1968) mitotic effector signals from the central comparator might be transmitted by some macroglobulin, whereas afferent information would be carried to the centre by lipoproteins. Similar views have been expressed by Szent-Györgi (1968) who suggested the existence of two antagonistic substances, a promoter of cell division called 'promine' and an inhibitor of growth, 'retine', which he tentatively identified with glyoxalase and methylglyoxal, respectively.

Saetren (1956) was the first to show that a crude extract from a rat kidney exerted an antimitotic activity when injected intraperitoneally. Since then Saetren's experiments have been repeated by several authors, with similar results (Williams, 1962; Goss, 1963; Saetren, 1963; Roels, 1965) although in some cases the inhibition of mitosis by the extracts could not be shown to be specific (Williams, 1962; Goss, 1963). Roels (1969) has critically reassessed the merit of these experiments and concluded that a renal extract may be an important factor in controlling compensatory renal growth. Recently, more evidence for a tissue-specific mitotic inhibitor of renal origin has been presented (Dicker, 1971*a, b*), though its identification has not yet been achieved.

Since the existence of an inhibitor of cell division of renal origin seems to have been demonstrated, one can assume that it is accompanied by another compound with the property of stimulating mitotic activity. Though little, if anything, is yet known about such a compound, it may be that a decrease of oxygen uptake accompanied by an enhanced rate of anaerobic glycolysis, as exists in the hydronephrotic kidney, are essential for its formation and release. After all, the rapid renal growth in the new-born rat occurs at a time when the rate of anaerobic glycolysis in the kidney is at its highest (Dicker & Shirley, 1971*a*).

To return to the concept of living control systems (Bayliss, 1966; Burch, 1968; Riggs, 1970), unilateral nephrectomy would result in halving the rate of information received by the 'central comparator' which then would

send effector signals to stimulate growth, which would then proceed until the amount of inhibitor is restored. As for compensatory renal growth following ureter ligation of the opposite kidney, it is conceivable that the combination of reduction of blood flow and of oxygen uptake, together with an enhanced rate of anaerobic glycolysis, result in a decreased production and/or release of inhibitor 'signals', which in turn would initiate growth of the contralateral organ.

Since, however, after both unilateral nephrectomy and ligation of one ureter there appears to be an immediate rise in renal blood flow of the contralateral kidney, and hence of glomerular filtration rate, it is likely that it is this increase which initiates the events which lead to subsequent hypertrophy, though the rate and magnitude of the compensatory growth is ultimately regulated by a system of control, involving the interaction of stimulating and inhibiting substances and of a central 'comparator'.

REFERENCES

BAYLISS, L. W. (1966). *Living Control Systems*. London: The English Universities Press.

BENITEZ, L. & SHAKA, J. A. (1964). Cell proliferation in experimental hydronephrosis and compensatory renal hyperplasia. *Am. J. Path.* **44**, 961–972.

BLOCK, M. A., WAKIM, K. G. & MANN, F. C. (1953). Appraisal of certain factors influencing compensatory renal hypertrophy. *Am. J. Physiol.* **172**, 60–66.

BURCH, P. R. J. (1968). *An Inquiry Concerning Growth, Disease and Ageing*. Edinburgh: Oliver and Boyd.

CARLSON, E. L. & SPARKS, H. V. (1970). Intrarenal distribution of blood flow during elevation of ureteral pressure in dogs. *Circulation Res.* **26**, 601–610.

CRANE, W. A. J. & DUTTA, L. P. (1963). The utilisation of tritiated thymidine for deoxyribonucleic acid synthesis by the lesions of experimental hypertension in rats. *J. Path. Bact.* **86**, 83–97.

CRANE, W. A. J. & INGLE, D. J. (1964). Tritiated thymidine uptake in rat hypertension. *Archs Path.* **78**, 209–221.

DICKER, S. E. (1949). Effect of the protein content of the diet on the glomerular filtration rate of young and adult rats. *J. Physiol.* **108**, 197–202.

DICKER, S. E. (1971a). Factors influencing compensatory renal hyperplasia. *J. Physiol.* **214**, 14–15P.

DICKER, S. E. (1971b). Inhibition of compensatory renal growth by substances from the kidney, in rats. *J. Physiol.* **218**, 62–63P.

DICKER, S. E. & HELLER, H. (1945). The mechanisms of water diuresis in normal rats and rabbits as analysed by inulin and diodone clearances. *J. Physiol.* **103**, 449–460.

DICKER, S. E. & SHIRLEY, D. G. (1971a). Rates of oxygen consumption and of anaerobic glycolysis in renal cortex and medulla of adult and new-born rats and guinea-pigs. *J. Physiol.* **212**, 235–244.

DICKER, S. E. & SHIRLEY, D. G. (1971b). Mechanism of compensatory renal hypertrophy. *J. Physiol.* **219**, 507–523.

FIDA, B. & CERRUTI, G. B. (1960). Il rene superstite dopo mononephrectomic. *Minerva nefrol.* **7**, 16–19.

FORTE, L. & LANDON, E. J. (1968). Aldosterone-induced RNA synthesis in the adrenalectomized rat kidney. *Biochim. biophys. Acta* **157**, 303–309.

FRANKLIN, S. S. & MERRILL, J. P. (1960). The kidney in health; the nephron in disease. *Am. J. Med.* **28**, 1–7.

FRIEDMAN, S. M., POLLEY, J. T. & FRIEDMAN, C. L. (1947). The clearance of inulin and sodium p-aminohippurate in the rat. *Am. J. Physiol.* **150**, 340–352.

GOSS, R. J. (1963). Mitotic responses of the compensating rat kidney to injections of tissue homogenates. *Cancer Res.* **23**, 1031–1035.

GOSS, R. J. & DITTMER, J. E. (1969). Compensatory renal hypertrophy: problems and prospects. In *Compensatory Renal Hypertrophy*, ed. NOWINSKI, W. W. & Goss, R. J. London: Academic Press.

GOSS, R. J. & RANKIN, M. (1960). Physiological factors affecting compensatory renal hyperplasia in the rat. *J. exp. Zool.* **145**, 209–216.

HEIDEMAN, D. H. & ROSENBAUM, H. D. (1970). A study of renal size after contralateral nephrectomy. *Radiology* **94**, 599–601.

HERDMAN, J. P. & JACO, N. T. (1950). Renal circulation in experimental hydronephrosis. *Br. J. Urol.* **22**, 52–55.

HERLANT, M. (1948). Activité mitotique des cellules rénales au cours de l'hydronéphrose unilatérale. *Bull. Acad. Med. Belg.* **13**, 315–330.

HINMAN, F. (1922). Renal counterbalance. An experimental and clinical study with reference to the significance of disuse atrophy. *Trans. Am. Ass. Genito-Urin. Surg.* **15**, 280–284.

IDBOHRN, H. & MUREN, A. (1956). Renal blood flow in experimental hydronephrosis. *Acta physiol. scand.* **38**, 200–206.

JACOBY, F. (1953). Mitotic activity in the gall-bladder epithelium of the guinea-pig after ligation of the common bile duct. *J. Physiol.* **119**, 21–22*P*.

JACOBY, F. (1959). In *Mitogenesis, A Symposium*, pp. 55–62, ed. DUCOFF, H. S. & EHRET, C. F. Chicago: University of Chicago Press.

JOHNSON, H. A. (1969). Cytoplasmic response to overwork. In *Compensatory Renal Hypertrophy*, ed. NOWINSKI, W. W. & Goss, R. J. London: Academic Press.

KROHN, A. G., PENG, B. B. K., ANTELL, H. I., STEIN, S. & WATERHOUSE, K. (1970). Compensatory renal hypertrophy: the role of immediate vascular changes in its production. *J. Urol.* **103**, 564–568.

MACKAY, E. M. (1932). Kidney weight, body size and renal function. *Archs intern. Med.* **50**, 590–594.

MACKAY, L. L. & MACKAY, E. M. (1927). Factors which determine renal weight. II. Age. *Am. J. Physiol.* **83**, 191–195.

MALT, R. A. (1969). RNA metabolism in compensatory renal growth. In *Compensatory Renal Hypertrophy*, ed. NOWINSKI, W. W. & Goss, R. J. London: Academic Press.

MASON, R. C. & EWALD, B. H. (1965). Studies on compensatory renal hypertrophy. I. Effect of unilateral ureteral ligation and transection. *Proc. Soc. exp. Biol. Med.* **120**, 210–214.

MORASKI, R. (1966). Renal hyperplasia in the intact rat. *Proc. Soc. exp. Biol. Med.* **121**, 838–840.

OGDEN, D. A. (1967). Donor and recipient function 2 to 4 years after renal homotransplantation. A paired study of 28 cases. *Ann. intern. Med.* **67**, 998–1006.

RIGGS, D. S. (1970). *Control Theory and Physiological Feedback Mechanisms*. Baltimore: Williams and Wilkins.

ROELS, F. (1965). Inhibition de l'activité mitotique au cours de l'hypertrophie compensatrice du rein par injection d'homogénats rénaux. *C. r. Séanc. Soc. Biol.* **159**, 495–497.

ROELS, F. (1969). Influence of homogenates of compensatory renal hyperplasia: inconsistence of results. In *Compensatory Renal Hypertrophy*, ed. NOWINSKI, W. A. & GOSS, R. J. London: Academic Press.

ROUS, S. N. & WAKIM, K. G. (1967). Kidney function before, during and after compensatory hypertrophy. *J. Urol.* **98**, 30–35.

ROYCE, P. C. (1963). Inhibition of renal growth following unilateral nephrectomy in the rat. *Proc. Soc. exp. Biol. Med.* **113**, 1046–1049.

SAETREN, H. (1956). A principle of autoregulation of growth. Production of organ specific mitosis-inhibitors in kidney and liver. *Expl cell Res.* **11**, 229–232.

SAETREN, H. (1963). The organ specific growth inhibition of the tubule cells of the rat's kidney. *Acta chem. scand.* **17**, 889.

SELKURT, E. E. (1963). Effect of ureteral blockade on renal blood flow and urinary concentrating ability. *Am. J. Physiol.* **205**, 286–292.

SIMPSON, D. P. (1961). Hyperplasia after unilateral nephrectomy and role of excretory load in its production. *Am. J. Physiol.* **201**, 517–522.

SMITH, H. W. (1951). *The Kidney Structure and Function in Health and Disease.* Oxford: University Press.

STEWART, G. N. (1921). Possible relations of the weight of the lungs and other organs to body-weight and surface area (in dogs). *Am. J. Physiol.* **58**, 45–52.

SUKI, W. N., GUTHRIE, A. G., MARTINEZ-MALDONADO, M. & EKNOYON, G. (1971). Effects of ureteral pressure elevation on renal haemodynamics and urine concentration. *Am. J. Physiol.* **220**, 38–43.

SZENT-GYÖRGY, A. (1968). *Bioelectronics. A Study in Cellular Regulations, Defense and Cancer.* London: Academic Press.

TAYLOR, F. B., DRURY, D. R. & ADDIS, T. (1923). The regulation of renal activity. The relation between the rate of urea excretion and the size of the kidneys. *Am. J. Physiol.* **65**, 55–61.

VANCURA, P., SHARP, G. W. G. & MALT, R. A. (1971). Kinetics of RNA synthesis in toad bladder epithelium: action of aldosterone during the latent period. *J. clin. Invest.* **50**, 543–551.

VENDRELY, R. (1955). The deoxyribonucleic acid content of the nucleus. In *The Nucleic Acids*, vol. II, pp. 155–180, ed. CHARGAFF, E. & DAVIDSON, J. N. New York: Academic Press.

WALD, H. (1937). The weight of normal adult human kidneys and its variability. *Archs Path.* **23**, 493-500.

WILLIAMS, G. E. G. (1962). Studies in the control of compensatory hyperplasia of the kidney in the rat. *Lab. Invest.* **11**, 1295–1302.